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*Published in:*
Langmuir

*DOI:*
10.1021/acs.langmuir.9b01989



*Publication date:*
2019

LANGMUIR Article
Cite This: Langmuir 2019, 35, 11821−11828
pubs.acs.org/Langmuir

# Reorganization from Kinetically Stable Aggregation States to Thermodynamically Stable Nanotubes of BINOL-Derived Amphiphiles in Water

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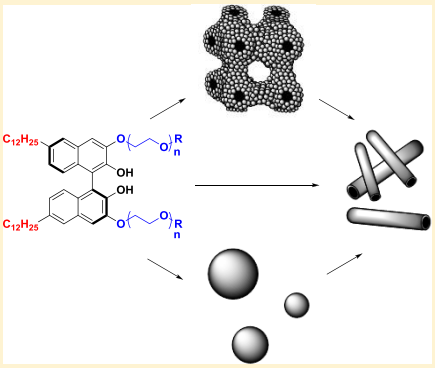
Supporting Information

**ABSTRACT:** The synthesis and self-assembly behavior of newly designed BINOL-based amphiphiles is presented. With minor structural modifications, the aggregation of these amphiphiles could be successfully tuned to form different types of assemblies in water, ranging from vesicles to cubic structures. Simple sonication induced the rearrangement of different kinetically stable aggregates into thermodynamically stable self-assembled nanotubes, as observed by cryo-TEM.




## INTRODUCTION

The design and exploitation of novel amphiphiles is of paramount importance for various applications,[1−6] among which catalysis in water is an emerging field.[7−12] The use of surfactants to promote reactivity in water has proven to be particularly interesting[10,13,14] and is reminiscent of the strategy employed by Nature where catalytic functions are embedded in compartmentalized systems. For example, in cellular membranes, the lipid bilayer encapsulates organic substrates and generates a favorable environment for reactions to take place.[15] The most used approach up to now has been to develop surfactants which self-assemble into micelles.[16−21] Due to their dynamic character, micellar reactors can enhance reaction rates and enantiomeric excesses under mild conditions with respect to most common organic solvents.[22−25]

The use of vesicular reactors[26−30] has been extensively explored in recent years. Compared to micelles, in selected examples, vesicles have exhibited an even greater influence over the reaction rate in water.[31,32] This suggests that mesoscopic differences in the morphology of the aggregates as well as variability in the self-assembly of soft materials can play an important role in catalysis. Reactivity and catalysis in more complex aggregates such as nanotubes and cubic structures have also recently received attention, showing fascinating opportunities to control transformations in water.[33−35] Considering that the nanostructure morphology has a major effect on reactivity, a key issue in the field of soft material catalysis is the ability to easily access different morphologies of self-assembled nanosystems. Ideally, a relevant change in aggregation should be performed without the necessity to redesign the amphiphile or perform major structural modifications.

The large variety of structures that can be obtained through the self-assembly of amphiphiles in water has been described by Israelachvili.[36] The difference in aggregate formation is based on the balance between hydrophilic and hydrophobic characters of the surfactant, resulting in the formation of micelles, vesicles, and inverted structures.[37−39] It has been reported that additional supramolecular interactions (such as $\pi-\pi$ stacking or hydrogen bonding) can influence these systems. These noncovalent interactions can lead to more complex morphologies such as nanotubes,[40] sheets,[41] ribbons,[42] and helicates.[43] In the challenging task to easily access multiple distinct morphologies of soft materials, simple modifications are a more practical and, therefore, preferable way to operate. To screen variations of the aggregate morphologies and achieve control over reactivity in self-assembled confined space systems, we needed to design a system in which minimal modifications in the last steps of the synthesis could result in a variety of structures, without performing extensive and time-consuming synthetic modifications.

To address this challenge, we designed amphiphilic systems based on 1,1-bi-2-naphthol (BINOL),[44] featuring a unique

Received: June 28, 2019
Revised: August 14, 2019
Published: August 19, 2019






DOI: 10.1021/acs.langmuir.9b01989
Langmuir 2019, 35, 11821−11828

atropoisomer biaryl core. These novel artificial amphiphiles were synthesized starting from enantiopure BINOL, which is commercially available at low cost in both enantiomeric forms. In addition, it has numerous applications in asymmetric catalysis and there are plentiful synthetic structural modifications to the BINOL scaffold, which are well documented in the literature.[45] The self-assembly of BINOL-based amphiphiles has been previously investigated in the solid state,[46] on silica support from the drying of a $CH_2Cl_2$ solution,[47] or BINOL has been included as a sodium salt in worm-like micelles.[48] The synthesis of chiral dendritic BINOL derivatives and their application in asymmetric hydrogenation in water has been achieved in a previous report,[49] although a material study was not performed. Moreover, amphiphilic polymers with BINOL moieties have been used for enantioselective recognition of amino acids in water,[50] and a recent example exploited a BINOL-based amphiphile for specific discrimination of arginine by gelation in water.[51] These reports are particularly relevant for the study of BINOL amphiphiles; however, the formation and tuning of different aggregates in water have to our knowledge not yet been explored.

The structural design of BINOL-based amphiphiles presented here is shown in Figure 1. Dodecyl chains were

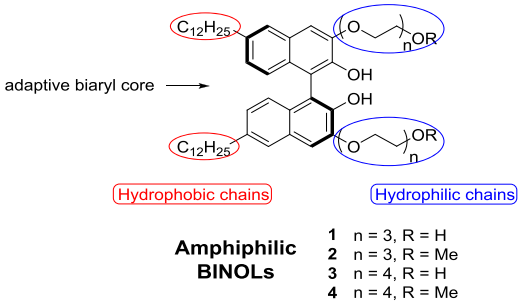



**Figure 1.** Design of amphiphilic BINOLs **1**–**4**.

chosen as the hydrophobic tails of these amphiphiles since they are known to efficiently induce self-assembly, driving amphiphiles to form a stable bilayer structure.[52] Hydrophilic poly(ethylene glycol) (PEG) chains were attached to allow for solubility in water, while preventing multiple layer stacking.[53−56] As the dodecyl chain is crucial for the self-assembly process, we decided to tune the hydrophilic component of the BINOL amphiphile. We envisioned that through modification of the PEG chains, the packing parameter of the amphiphile would be influenced,[36] therefore allowing the morphology of the self-assembled nanostructure to be regulated. An advantage of this design lies in the possibility to modify the terminal moiety of these novel surfactants through late-stage functionalization, allowing for the straightforward synthesis of a small family of compounds, which then translates to the formation of a range of self-assembled morphologies. Therefore, ethylene glycol chains with different lengths and terminal groups were attached to the BINOL core to obtain the four derivatives **1**–**4**, which were investigated in the present study (Figure 1).

Compounds **1** and **2** are amphiphilic BINOLs that contain triethylene glycol chains terminating with OH and OMe groups, respectively. Compounds **3** and **4** represent amphiphiles with tetraethylene glycol units ending with OH and OMe, respectively. By employing this simple approach as presented here, we provide an effective platform to easily access different aggregates characterized by the same scaffold, generating a potentially useful homochiral space in a soft material (the BINOL unit).

## EXPERIMENTAL SECTION

**Materials.** Chemicals were purchased from Aldrich. Solvents for extraction and chromatography were of technical grade. All solvents used in the reactions were dried using an SPS-system. All other reagents were recrystallized or distilled when necessary. Analytical TLC was performed with Merck silica gel 60 F254 plates and visualization was accomplished by UV light. Flash chromatography was carried out using Merck silica gel 60 (230−400 mesh ASTM). Components were visualized by staining with a solution of $KMnO_4$. NMR spectra were obtained using a Varian Unity Plus Varian-400 and a Varian Unity Plus Varian-500, operating at 399.93 and 499.86 MHz, respectively, for the $^1H$ nucleus or at 100.57 and 125.70 MHz, respectively, for the $^{13}C$ nucleus. Chemical shifts are reported in $\delta$ = units (ppm) relative to the residual protonated solvent signals of $CDCl_3$ ($^1H$ NMR: $\delta$ = 7.26 ppm) or at the carbon absorption in $CDCl_3$ ($^{13}C$ NMR: $\delta$ = 77.0 ppm). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. MS (EI) spectra were obtained with a Jeol JMS-600 spectrometer. A detailed description of the synthetic procedures and characterization is included in the Supporting Information.

**Methods.** *Sample Preparation.* In a 4 mL vial, 1 mL of a 2 mM solution of the compound (**1**−**4**) in technical grade $CHCl_3$ was placed. The solvent ($CHCl_3$) was slowly dried in a nitrogen flow and a thin film of the amphiphilic compound was formed, which was subsequently hydrated with double distilled water (1 mL).

*Sample Measurement.* Samples for cryo-TEM were prepared by depositing a few $\mu$L of the amphiphile solution on holey carbon-coated grids (Quantifoil 3.5/1, Quantifoil Micro Tools, Jena, Germany). After blotting the excess liquid, the grids were vitrified in liquid ethane (Vitrobot, FEI, Eindhoven, The Netherlands) and transferred to a Philips CM 120 or FEI Tecnai T20 cryo-electron microscope equipped with a Gatan model 626 cryo-stage operating at 120 and 200 keV, respectively. Micrographs were recorded under low-dose conditions with a slow-scan CCD camera. The bilayer thickness was measured on slightly defocused cryo-electron microscopy images to obtain maximal phase contrast.

*pH Dependence Measurement.* The pH of a water solution was adjusted with 100 mM aq. HCl or aq. NaOH and measured by a pH meter in a 500 $\mu$L solution. A dry film of the amphiphile was hydrated with water at the desired pH followed by 3 freeze−thaw cycles to favor the self-assembly process.

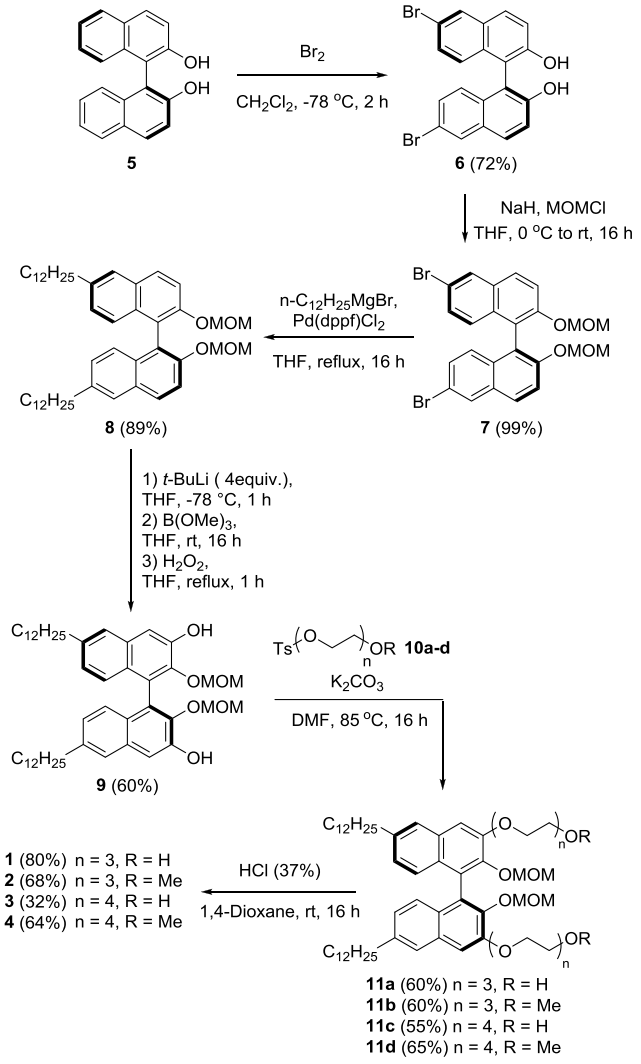
## RESULTS AND DISCUSSION

The synthesis of the desired amphiphilic BINOL derivatives (Scheme 1) started with dibromination of enantiopure (*S*)-BINOL **5** at the 6,6′-positions.[57] The phenolic moieties of the obtained dibromo compound **6** were subsequently protected with methoxymethyl (MOM) groups, which have the added benefit of being convenient ortho-directing groups for further functionalization. The introduction of two dodecyl chains to compound **7** could be achieved by several approaches, among which a Kumada cross-coupling reaction[58] allows for easy operation and gram-scale synthesis of **8** in good yield (89%). The obtained dialkylated compound **8** was then treated with *t*-BuLi and reacted with freshly distilled $B(OMe)_3$, to provide the diborylated intermediate, which was used without further purification. After the addition of $H_2O_2$, the mixture was heated at reflux in THF for 1 h to generate the dihydroxyl compound **9** in 60% isolated yield over two steps. Four different OTs-substituted PEG chains (**10a**−**d**), prepared according to reported procedures,[59−62] were reacted with **9** in the presence of a base to afford the corresponding BINOL derivatives **11a**−**d**. After deprotection of the MOM groups



DOI: 10.1021/acs.langmuir.9b01989
Langmuir 2019, 35, 11821−11828

**Scheme 1. Synthesis of Amphiphilic BINOLs 1−4**




under acidic conditions and column chromatography, the designed BINOL amphiphiles were obtained and fully characterized via $^{1}$H NMR, $^{13}$C NMR, and HRMS (see the Supporting Information).

With four BINOL amphiphiles in hand, the effect of different hydrophilic substituents on the self-assembly of the amphiphiles in water was studied by cryo transmission electron microscopy (cryo-TEM). Compound **2**, which contains the shortest PEG chains and is OMe terminated, is the least hydrophilic among the synthesized amphiphiles. As expected, this compound showed the poorest water solubility, and no aggregation was observed. In contrast, the other amphiphiles, with a longer PEG chain and/or OH terminality, present enhanced solubility in the aqueous environment, which allows for the observation of well-defined structures. Amphiphilic BINOL **1**, which features a triethylene glycol chain terminated with a OH, was found to assemble into well-defined and tightly packed cubic structures (Figure 2a).[63] This self-assembled structure is characterized by highly curved bilayers tightly organized in a bi-continuous phase, presenting a porous system, which is evident from the convolutions of the soft material reported in Figure 2a. On the contrary, BINOL **3** was found to self-assemble into vesicles. The different aggregated structures, i.e., vesicles, can be attributed to the increased

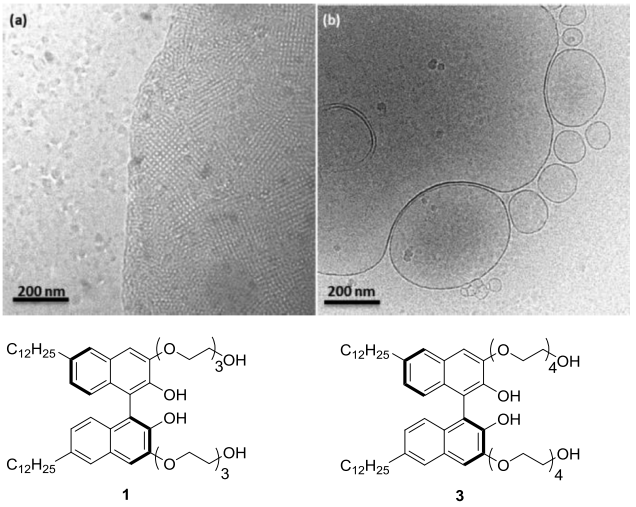



**Figure 2.** Cryo-TEM image of self-assembly in water of (a) BINOL **1** (cubic structure) and (b) BINOL **3** (vesicles).

hydrophilicity and larger headgroup surface area (smaller packing parameter) of **3** by extending one extra ethylene glycol unit compared to **1** (Figure 2b).[36,38]

As a consequence of the difference in the glycol chain terminal group with respect to compound **3** (OMe instead of OH), we expected to observe a difference in self-assembly of compound **4**. Most interestingly, cryo-TEM studies of **4** revealed the formation of well-defined nanotubes (Figure 3),[64]

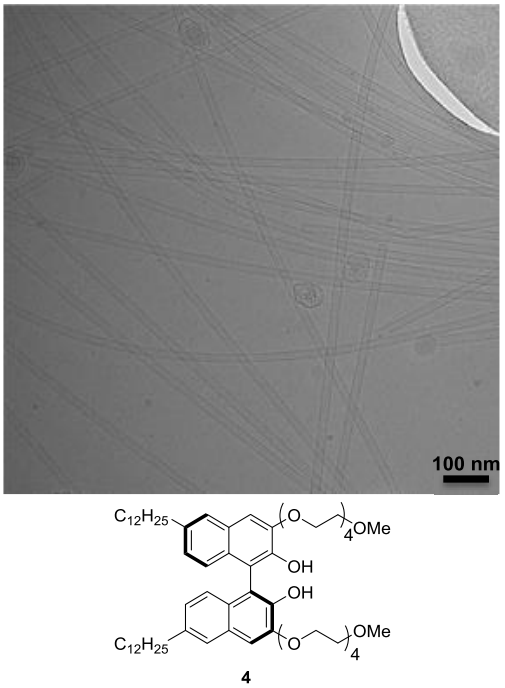



**Figure 3.** Cryo-TEM image of nanotubes upon self-assembly in water of BINOL **4**.

which differ from the usual structures whose outcome is predicted by the packing parameter described by Israelachvili (i.e., micelles, vesicles, planar bilayers, and inverted structures).[36]

The nanotubes visible in Figure 3 are several micrometers in length and present uniform diameters of 20 nm. The width of



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Langmuir 2019, 35, 11821−11828

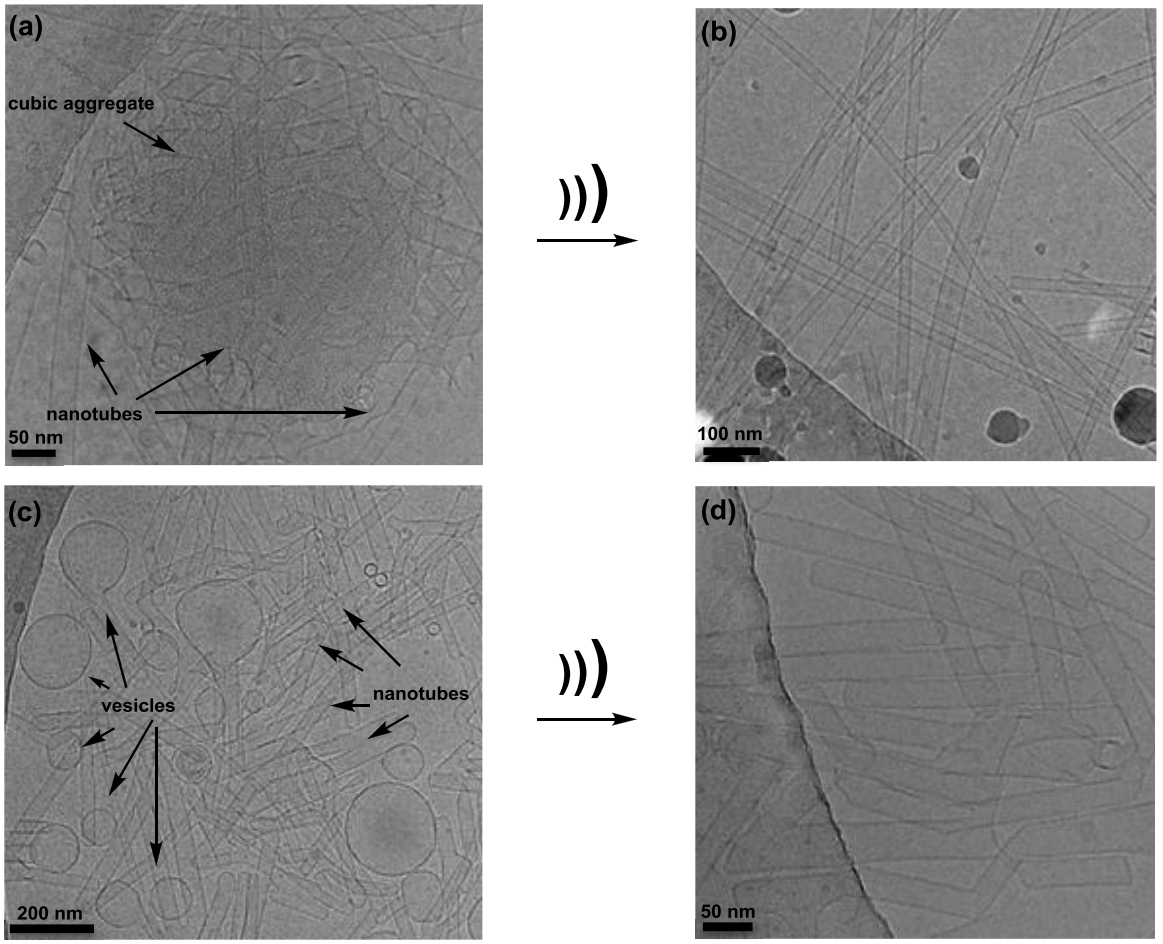


**Figure 4.** (a) Self-assembly of BINOL **1**, co-existence of cubic structure and nanotubes; (b) self-assembly of BINOL **1**, only nanotubes after sonication; (c) self-assembly of BINOL **3**, co-existence of vesicles and nanotubes; (d) self-assembly of BINOL **3**, only nanotubes after sonication.

the wall of the tubes was found to be around 4 nm, which, based on the dimensions of **4**, suggests the formation of a bilayer.[36] The simplicity of preparing such well-defined structures is worth noting. The addition of water to a dry thin film of **4** immediately resulted in the nanotube formation, without the need for additional operations.

Since BINOLs are weak acids, deprotonation at higher pH can potentially lead to a change in the packing parameter due to charge repulsion. No significant change of the structures could be observed by hydrating compound **4** in a pH range from 5 to 9, suggesting that the obtained nanotubes are stable within the above-mentioned pH range (Figure S1). In addition, when a dry thin film of **4** was directly hydrated at pH 10, co-existence of nanotubes and vesicles was observed (Figure S2). The mixture was subsequently neutralized to pH 7, in situ, and only tubular structures were observed (Figure S3). Bringing the solution again to pH 10, the tubular structures remained intact. The above experiment suggests that the nanotube structure is the thermodynamically more stable assembly of the system.

The fact that the aggregates do not revert to a vesicular assembly upon making the solution more basic is also a hint that deprotonation is more difficult once the nanotubes are formed.[65] Further investigating amphiphiles **1** and **3**, it was curiously observed that the aggregation of these compounds changed over time, by simply allowing the samples to stand for a few hours after preparation. In all samples of the above-mentioned amphiphiles, the formation of nanotubular structures was clearly observed (Figure 4).

Submitting the samples to ultrasound stimulation has accelerated this process. In the case of compound **1**, the first aggregate observed was indeed a cubic structure (Figure 2a), which underwent a rearrangement resulting in the formation of nanotubes. With the help of simple sonication, we could accelerate the process of reorganization. Using cryo-TEM, we could effectively follow the intermediate step showing co-existence of nanotubes and cubic aggregates (Figure 4a) and further sonication of the sample resulted in the formation of nanotubes exclusively (Figure 4b). Similarly, compound **3** that first aggregated into vesicles (Figure 2b) showed the presence of nanotubes and vesicles simultaneously in an intermediate stage (Figure 4c), which could be further pushed to the formation of only nanotubes by the use of sonication (Figure 4d).

In some specific cases, we can observe via cryo-TEM, the growth of nanotubes from the single vesicles themselves (Figure 5).

Upon submitting the formed nanotubes of these samples to environmental changes (higher pH, further sonication, higher temperature), no changes in the morphologies of such aggregates were observed, indicating that even in this case, the nanotubular structures formed are the thermodynamically most stable assembly of the system. As noted for compound **4**,



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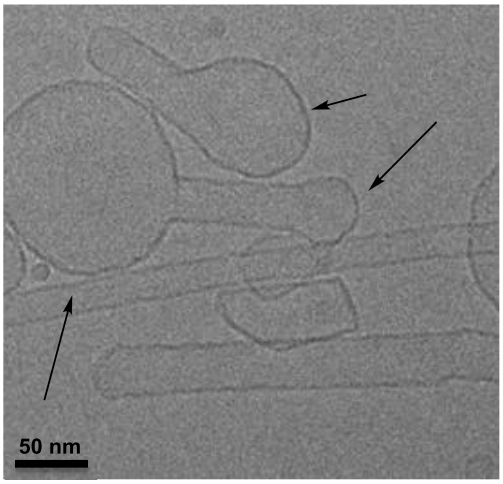



**Figure 5.** Detail of the self-assembled structures of compound **3** after 2 h standing at room temperature. Arrows are pointing to the elongated vesicles.

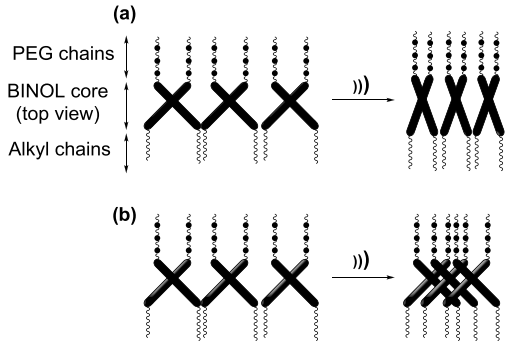



**Figure 6.** (a) Schematic representation of the hypothetical change in torsion angle of the binaphthyl core of BINOL amphiphiles; (b) schematic representation of the hypothetical reorganization of the packing of BINOL amphiphiles.

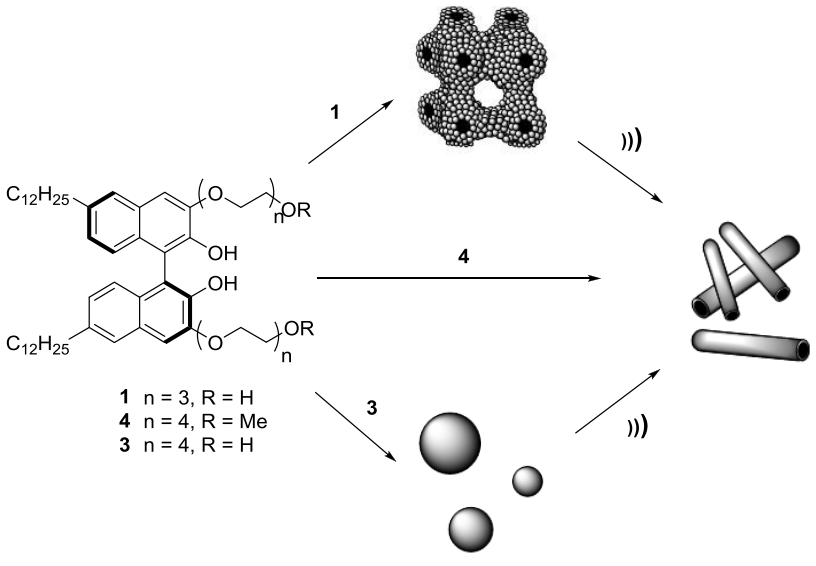
the nanotubular aggregates show incredible stability with respect to external stimuli.

Evidently, these novel BINOL-based amphiphiles show various morphologies in the early stage of the self-assembly process (Scheme 2), presenting distinct differences in the structure as a function of the PEG chain length and terminating substituents. Via the simple use of ultrasound stimulation, these kinetically formed aggregates are driven to the formation of nanotubes, probably as a result of the stacking of the BINOL aromatic core of the amphiphile. As a qualitative hypothesis, we anticipate that the torsion angle of the binaphthyl core adapts in the soft material as a result of ultrasound stimulation, causing the surfactant to assume a different morphology and stimulating the conversion from kinetic to thermodynamic self-assemblies (Figure 6a). Alternatively, sonication could help bring the BINOL amphiphiles closer together favoring their packing. Due to the stability of the nanotubes under a range of stimuli and the consistency in the packing of the different amphiphiles, forces other than hydrophobic interactions must be involved in the packing (for example $\pi-\pi$ stacking). Although we are not at the moment able to provide a theoretical or experimental proof of this model, the nature of the key interactions and their effect on the packing is currently under investigation in our laboratories.

## CONCLUSIONS

In conclusion, by simple modifications, we could easily tune the self-assembly behavior of novel artificial BINOL-based amphiphiles. By changing the length and terminal moieties of the PEG chain, we were able to control the balance between hydrophilic and hydrophobic characters of the surfactants. An additional PEG unit and/or the introduction of OH groups enhances the solubility of the amphiphile in water, hence controlling the self-assembled morphologies and greatly influencing the difference in structures observed, even though the differences in substitution are small. Distinct self-assembled aggregates have been observed, ranging from cubic structures to vesicles. These kinetically formed aggregates are driven to a thermodynamically more stable state by simple ultrasound stimulation, resulting in the formation of nanotubes regardless of the substitution of the chain length of the amphiphiles. This study demonstrates that by rational design, important organic

**Scheme 2. Schematic Representation of the Self-Assembly of Amphiphilic BINOLs 1, 3, and 4**






DOI: 10.1021/acs.langmuir.9b01989
*Langmuir* 2019, 35, 11821−11828

ligands such as BINOL derivatives can be assembled into tightly packed, well-organized supramolecular structures in water. Their aggregation morphologies can be addressed during different stages of aggregation, i.e., the formation of kinetically or thermodynamically stable aggregates. The obtained structures provide a first step toward the effective control of reactivity in self-assembled nanosystems by influencing their morphology. Our work contributes to generate a platform for further applications in asymmetric catalysis in self-assembled bilayers and dynamic responsive soft materials.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.langmuir.9b01989.

Synthetic procedures, $^{1}H$ and $^{13}C$ NMR spectra and pH-dependent cryo-TEM (PDF)

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### Author Contributions

The manuscript was written through contributions of all of the authors. All of the authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

B.L.F. acknowledges financial support from The Netherlands Organisation for Scientific Research, the European Research Council (ERC Advanced Grant 227897), the Royal Netherland Academy of Arts and Sciences (KNAW), and the Ministry of Education, Culture, and Science (Gravitation program 024.601035).

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